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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

ILLUMINA, INC. and
ILLUMINA CAMBRIDGE LTD.,

Plaintiffs,

v.

BGI GENOMICS CO., LTD.,
BGI AMERICAS CORP.,
MGI TECH CO., LTD.,
MGI AMERICAS, INC., and
COMPLETE GENOMICS INC.,

Defendants.

COMPLETE GENOMICS INC.,

Counterclaim-Plaintiff,

v.

ILLUMINA, INC., and
ILLUMINA CAMBRIDGE LTD.,

Counterclaim-Defendants.

Case No. 3:19-cv-03770-WHO
Case No. 3:20-cv-01465-WHO

PLAINTIFFS' NOTICE OF MOTION AND RENEWED MOTION FOR JUDGMENT AS A MATTER OF LAW

Judge William H. Orrick

Date: March 2, 2022
Time: 2:00 PM

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NOTICE OF MOTION

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE that as soon as the Court may practically hear before the Honorable William H. Orrick, United States District Court, Northern District of California, 450 Golden Gate Ave., Courtroom 2, San Francisco, CA 94102, plaintiffs Illumina, Inc. and Illumina Cambridge LTD. (collectively "Illumina"), will and hereby does move for judgment as a matter of law that Defendants Complete Genomics, Inc., BGI Genomics Co. Ltd., BGI Americas Corp., MGI Tech Co., Ltd., and MGI Americas, Inc. (collectively "BGI") have failed to meet their burden to prove that Claim 1 of U.S. Patent No. 10,480,025 ("the '025 Patent"), and Claim 3 of U.S. Patent No. 7,541,444 ("the '444 Patent") are invalid on as obvious under 35 U.S.C. § 103, or in the alternative that a new trial on those claims is warranted.

This motion is based on this notice and supporting memorandum, the trial record, and such other matters of which the Court may take judicial notice.

RELIEF REQUESTED

Illumina respectfully seeks an order that Claim 1 of the '025 Patent and Claim 3 of the '444 Patent are not invalid, or in the alternative a new trial on the issue of validity of Claim 1 of the '025 Patent and Claim 3 of the '444 Patent.

MEMORANDUM OF POINTS AND AUTHORITIES

I. INTRODUCTION

Illumina hereby renews its motion for judgment as a matter of law ("JMOL") that BGI has failed to meet its burden of proving by clear and convincing evidence that Claim 1 of the '025 Patent and Claim 3 of the '444 Patent are invalid as obvious under 35 U.S.C. § 103. FRCP 50(b). In the alternative, Illumina moves for a new trial on the issue of validity of Claim 1 of the '025 Patent and Claim 3 of the '444 Patent. FRCP 59.

With respect to Claim 1 of the '025 Patent, BGI's only obviousness theory supporting the jury's verdict is contrary to the repeated legal conclusion by numerous judges that it would not have been obvious to use Zavgorodny's azidomethyl for sequencing-by-synthesis ("SBS"). BGI inexplicably ignored the overwhelming objective indicia of non-obviousness confirming the validity of the patents, which its own expert admitted had to be considered for a proper obviousness analysis. On this record, there simply is not clear and convincing evidence to support the legal conclusion in the verdict that this claim is invalid. As a second independent ground for upholding the validity of this claim, BGI failed to demonstrate by clear and convincing evidence that "base linked to a detectable label via a cleavable linker" limitation is present in the prior art or would have been obvious to combine with all of the other claim requirements.

For Claim 3 of '444 Patent, BGI's deliberate failure to address the overwhelming objective indicia of non-obviousness – even though they legally must be considered – likewise requires upholding the validity of this claim. BGI's incomplete obviousness analysis is legally inadequate also because the parties agreed that the skilled artisan for this patent would be focused on DNA sequencing and analysis – which is a far cry from antiviral drug development. The motion should be granted in full.

II. BACKGROUND

Illumina's azido patent rights are valid and battle-tested. In 2016, another multi-national life-sciences company, Qiagen N.V., attempted to introduce sequencers using Illumina's patented azido chemistry. *See* TX1783 at 001-002. Before doing so, it attempted to challenge the '537 Patent before the PTAB. *See* TX1803. The PTAB upheld Illumina's patent after a trial. *Id*. Qiagen appealed to the Federal Circuit, which also upheld Illumina's patent. *See* TX0413. In doing so, the Federal Circuit

relied on the PTAB's finding that the use of an azidomethyl protecting group for SBS would have been non-obvious to a person of ordinary skill in the art. *Id.* at 015 ("[A] person of ordinary skill in this field would not have been motivated to use the azidomethyl group of Zavgorodny[1] as a 'protecting group [that] can be modified or removed to expose a 3′ [hydroxyl] group' of a nucleic acid molecule, as the claim requires. This is so because the azidomethyl group would have been expected to perform inefficiently in that role.").

Although its validity challenges failed before the PTAB, Qiagen attempted to nevertheless introduce its infringing sequencers into the United States. TX1783 at 001-002. In doing so, it attempted to argue that there were still substantial questions as to the validity of Illumina's '537 patent. Judge Alsup thoroughly rejected Qiagen's invalidity arguments and found that it is likely the validity of Illumina's patent rights would be upheld. TX1783; Trial Tr. 876:13-877:21. Because of the strength of Illumina's azido patent rights, Judge Alsup found that Illumina presented a "powerful" case for an injunction. TX1783 at 016:5.

In 2017, Defendants invested in two IPRs to try to challenge the '537 Patent despite Qiagen's previous failures. *See* TX0984; TX0985. In support, BGI submitted 60 prior art references to the PTAB. Trial Tr. 1022:16-19. The PTAB rejected Defendants' challenges because one was duplicative of Qiagen's prior failed IPR and their second IPR failed to show a reasonable likelihood on the merits that the '537 Patent was invalid. *See* TX0986; TX0987; *see also* Trial Tr. 1022:5-15 (BGI's IPR challenges were "substantially basically identical" to Qiagen's challenges).

On June 15, 2021, this Court, in granting Illumina's Motion for Preliminary Injunctions, found that "BGI has not demonstrated a substantial question as to the invalidity of Illumina's patents with respect to obviousness" because "BGI has not adequately established that a POSITA would have been motivated to combine Parce[2] and Zavgorodny (or both Zavgorodny[3] references) or that a POSITA would expect a reasonable likelihood of success" and "a closer look at BGI's arguments confirms that

[1] JTX051 (also referred to as Zavgorodny 1991).

[2] TX3236.

[3] The second Zavgorodny reference is Zavgorodny 2000 (JTX007).

the current obviousness argument is akin to those that have already been rejected by prior courts and the IPR Board." Dkt. No.[4] 185 at 12-13, 15-17. BGI included its antiviral obviousness theory for the '444 Patent, which the Court also rejected. Dkt. No. 119-4 at 21-22; Dkt. No. 145-3 at 3.

Illumina's expert, Dr. Floyd Romesberg, testified that the history of these prior challenges in other Courts were directly relevant to BGI's invalidly arguments here. *See* Trial Tr. 1020:9-21. Although the prior challenges were focused on the '537 patent, the reasoning of the 10 judges who previously reviewed that patent applies to all of the asserted patents in the case. *See* Trial. Tr. 1020:9-1021:7. This is because all of the patents-in-suit "claim the azidomethyl nucleotide invention, and so the judges' opinion about those would be the same in each patent," because the reasoning directly addresses BGI's sequencing obviousness theory. *Id.* 1021:8-15. BGI's expert did not consider these prior rulings (or the objective indicia) or attempt to explain why they were wrong because they were outside his assignment, even though he knew they should be considered. Trial Tr. 868:5-11, 879:24-880:11.

At trial, BGI repeated these same past arguments without attempting to explain why the ten judges that had considered this same obviousness theory were wrong. BGI also attempted to pivot for the '444 Patent to an antiviral theory that is flatly inconsistent with the objective indicia and outside the motivations of a skilled artisan in the sequencing and DNA analysis field. The jury returned a verdict of willful infringement, and found that all the asserted claims were valid, with the exception of Claim 1 of the '025 Patent and Claim 3 of the '444 Patent.

III. LEGAL STANDARD

A. Judgment As A Matter Of Law

"A district court may grant a motion for judgment as a matter of law pursuant to Rule 50(a) or (b) 'when the evidence presented at trial permits only one reasonable conclusion,' *i.e.*, 'if no reasonable juror could find in the non-moving party's favor.'" *Nichols v. City of San Jose*, 2017 WL 3007072, at *1 (quoting *Torres v. City of Los Angeles*, 548 F.3d 1197, 1205 (9th Cir. 2008)) (internal quotation marks and citations omitted).

[4] All citations to the docket refer to the docket in Case No. 3:19-cv-03770-WHO, unless otherwise specified.

Pursuant to Rule 59, a "court may, on motion, grant a new trial on all or some of the issues—and to any party" in a jury trial "for any reason for which a new trial has heretofore been granted in an action at law in federal court." FRCP 59. "Historically recognized grounds [for granting new trial] include, but are not limited to, claims that the verdict is against the weight of the evidence, that the damages are excessive, or that, for other reasons, the trial was not fair to the party moving." *Molski v. M.J. Cable, Inc.*, 481 F.3d 724, 729 (9th Cir. 2007).

B. Obviousness

"Obviousness is a question of law based on underlying facts. When reviewing a denial of JMOL of obviousness, where there is a black box jury verdict, as is the case here, we presume the jury resolved underlying factual disputes in favor of the verdict winner and leave those presumed findings undisturbed if supported by substantial evidence. We then examine the legal conclusion de novo in light of those facts." *Apple Inc. v. Samsung Elecs. Co., Ltd.,* 839 F.3d 1034, 1047 (Fed. Cir. 2016) (citing *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1356–57 (Fed. Cir. 2012)).

The patent challenger has the "burden to prove that all claimed limitations are disclosed in the prior art" and demonstrate that a "skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success." *PAR Pharmaceutical, Inc. v. TWI Pharmaceuticals, Inc.*, 773 F.3d 1186, 1192-1194 (Fed. Cir. 2014); *see also In re Stepan Co.,* 868 F.3d 1342, 1345-1346 (Fed. Cir. 2017) ("An obviousness determination requires finding both 'that a skilled artisan would have been motivated to combine the teachings of the prior art . . . and that the skilled artisan would have had a reasonable expectation of success in doing so.'") (citing *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.,* 821 F.3d 1359, 1367-68 (Fed. Cir. 2016)). "A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to reach a conclusion of obviousness until all those factors are considered," including "[o]bjective indicia of nonobviousness" which "must be considered in every case where present." *Apple Inc.*, 839 F.3d at 1048.

IV. ARGUMENT

The Asserted Patents are entitled to a presumption of validity. *See Microsoft Corp. v. I4I Ltd. P'ship*, 564 U.S. 91, 100 (2011). BGI, as the patent challenger, has the burden of establishing the legal

conclusion of obviousness based on clear and convincing evidence. *Id.*; *see also* Trial Tr. 865:3-7.

A. There Is Not Clear And Convincing Evidence To Support The Legal Conclusion In The Jury's Verdict That Claim 1 Of The '025 Patent Is Invalid As Obvious

With the sole exception of Claim 1 of the '025 Patent, the jury verdict ***upheld*** the validity of the claims of the '025 Patent, '537 Patent, and '200 Patents – which BGI had grouped together and termed the narrow patents because they required linkers and/or labels. BGI did not single out Claim 1 of the '025 Patent in its obviousness theory or offer any basis for the jury to treat that claim differently than the '537 Patent that had been upheld so many times (much less the 10 other claims in this group of patents that the jury upheld). Indeed, BGI did not present any tailored arguments to this claim. Instead, BGI and Dr. Metzker argued generally that "all three of these patents -- the '200, the '025, and the '537 -- are invalid in view of Parce, Zavgorodny, Kovacs, and/or Dower[5]." Trial Tr. 862:1-3.

In fact, Claim 1 includes additional limitations compared to many of the claims upheld by the jury. Claim 1 of the '025 Patent requires that the claimed nucleotide molecule must have "a ***base linked*** to a detectable label via a ***cleavable*** linker," a limitation BGI did not establish was obvious to include in its prior art combinations. BGI never established that a cleavable linker attached to the base is present in the prior art – much less that it would have been obvious to combine such a linker with the rest of the claimed chemical structure. Trial Tr. 800:9-13, 801:5-10. Because BGI did not attempt to tailor arguments to Claim 1 of the '025 Patent, it failed to carry its heavy burden of submitting clear and convincing evidence to meet that claim's unique requirements. The patent challenger has the "burden to prove that all claimed limitations are disclosed in the prior art." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014); *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006) (courts engage in an analysis of motivation to combine and reasonable expectation of success only if "all elements of an invention are found in a combination of prior art references.").

Moreover, regardless of the absence of a cleavable linked attached to the base, BGI's sequencing obviousness theory – the only theory BGI put forward for the '025 Patent – is not supported by clear and convincing and cannot support a legal conclusion of obviousness.

[5] Dower was not admitted into the record during trial and therefore cannot support BGI's obviousness theory.

1. BGI Failed To Prove That Any Of The Asserted Patents Are Obvious Over Sequencing Prior Art And There Is No Other Basis For The Jury's Verdict For Claim 1 Of The '025 Patent

BGI's only obviousness theory with respect to Claim 1 of the '025 Patent is that the claim is obvious in light of sequencing prior art – that it would have been obvious to create the claimed nucleotide for use in SBS. *See* Trial Tr. 862:4-11 ("[A] cleavable linker and a label . . . was one of the standard methods that were used in the SBS method."). As established below, the ultimate legal conclusion of obviousness is not supported by a theory that so many judges and the jury rejected in all the other instances in which it was presented.

The '537 Patent has been battle-tested, and the Patent Office has repeatedly found that it would not be obvious to combine Zavgorodny or other references disclosing azidomethyl with any "SBS" method. *See* § II; *see also* Trial Tr. 1022:9-15 (the validity arguments at issue at this trial are with the exception of "a few small changes of substituting in the sequence by synthesis reference for another, they're basically the same thing."). Dr. Romesberg testified that "even though the prior legal proceedings were focused on the '537 patent," "the reasoning of these ten judges appl[ies] to all of the asserted patents in this case." *See* Trial Tr. 1021:4-7; *see also* Dkt. No. 185 at 15-16 (this Court rejecting the same sequencing obviousness theory at the preliminary injunction stage). This is especially true of the '025 Patent, which claims a cleavable linker and label that "was one of the standard methods that were used in the SBS method" according to Dr. Metkzer. Trial Tr. 862:4-11. Yet, Dr. Metzker did not "opine whether there was any mistake by the Patent Office of any of the IPRs in considering that theory of Zavgorodny taught an azido blocking group and SBS was known and you could combine the two was because that wasn't within the scope of [his] assignment." Trial Tr. 868:12-17. Dr. Metzker's conspicuous lack of explanation as to why the previous Court's assessment of the same sequencing obviousness theory was incorrect or distinguishable from BGI's theory in this case establishes that BGI has not presented clear and convincing evidence of obviousness at trial. Additionally, Dr. Drmanac's lay testimony regarding the alleged mistake made by the Patent Office cannot remedy this failing and support a legal conclusion of obviousness, especially in light of BGI's failure to attempt to correct that supposed mistake by filing its own IPR and that the admissibility of this testimony was limited to his state of mind. Trial Tr. 614:4-618:6.

The rejection of BGI's sequencing obviousness theory by the jury in this case and the ten judges previously is further supported by the overwhelming weight of the evidence presented by Illumina at trial, and the lack of clear and convincing evidence presented by BGI. Without contradiction, Dr. Romesberg established that Zavgorodny's removal conditions would ***not*** have been compatible with SBS and DNA. *See* Trial Tr. 1030:9-17. Even if a POSITA would have found Zavgorodny, they "[t]hey would have picked it up and put it down," because it does not address the question the POSITA is focused on, "trying to get sequencing by synthesis to work." Trial Tr. 1028:19-1029:21. As Dr. Metzker admitted, "Zavgorodny does not describe sequencing by synthesis." Trial Tr. 902:9-11. This is further supported by potent objective evidence, including from Dr. Metzker himself, who testified he tried dozens of different blocking groups "in search of a new reversible terminator that could be used in the SBS method" in the "2002-2003" time period and did not identify azidomethyl as a candidate. Trial Tr. 897:24-899:3; *see also id.* 893:23-894:9, 895:2-7; TX3258 (Dr. Metzker's paper noting there are "stringent requirements" for SBS nucleosides that "are formidable obstacles for the design and synthesis of the requisite analogs."). Dr. Metzker could not offer any viable why – if azidomethyl was an obvious blocking group – neither he nor any of the luminaries he worked with had even thought of it.

Beyond that, the record is replete with objective evidence of non-obviousness that BGI's obviousness case to the jury blatantly did not consider or contest. As described further below (*see* § IV.B.1), Dr. Metzker "ignored the objective evidence of nonobviousness," but nonetheless purported to "conclude[] that the asserted claims of the [asserted] patents were obvious," utterly failing to "consider all factors relevant to that ultimate question" of obviousness in order "to guard against this hindsight." *InTouch Technologies, Inc. v. VGO Communications, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014). Yet, the objective evidence that Dr. Metkzer ignored, showing a long-felt need, the failure of others, copying, industry praise, skepticism, and unexpected results, demonstrate that BGI failed to prove by clear and convincing evidence that Claim 1 of the '025 Patent is obvious.

The long-felt need evidence is compelling and unchallenged. In previously attempting to invalidate the claims, BGI argued that "[b]efore August 2002, nucleotide analog chemistry was a focus of significant scientific and commercial resources" "driven by immense market pressure," admitting

there was a long-felt need in the industry for a suitable blocking group. TX0984 at 031. The evidence showed the "increasing demands in the community for better sequencing systems" starting "in the early 1990s." Trial Tr. 888:10-12. This long-felt need was not met until a decade later, by Illumina's patented azidomethyl blocking group. In other words, despite a massive industry effort involving leading scientists and the fact that Zavgodorny was published in 1991, there is not a shred of evidence that anyone considered azidomethyl as a blocking group – much less that it was ***ever*** considered to be obvious by the many workers in the field.

The trial record also features unrebutted evidence of the failure of others. Dr. Metzker admitted that there was no one else "working with the azidomethyl as a protecting group between the time Zavgorodny was published until the Bentley paper" in 2008 – almost two decades of serious effort in the sequencing area. Trial Tr. 902:5-8; *see also id.* 896:8-15, 897:5-10, 904:14-19. Despite so many research groups working on the problem with so many different blocking groups, including Dr. Metzker himself, none were able to solve the problem that Illumina solved, demonstrating definitively that the patented inventions were not obvious to the researchers trying to solve the problem in the real-world. *See, e.g.*, Trial Tr. 1017:10-1019:1, 1057:9-24. Indeed, the failure of others in the industry to develop a suitable blocking group for SBS aside from azidomethyl continued long after the patents were filed. BGI itself "was trying to work very hard, trying very hard" to "try to find an alternative to the patented azido." Trial Tr. 322:20-323:3; TX0326 ("new critical projects (e.g. non-azido block …"), TX0687 ("M.V. team must come up with alternative to azido ASAP.").

The long-felt need and failure of others to find an alternative to azidomethyl led workers to blatantly copy Illumina's azidomethyl blocking group. After discovering that Illumina used azidomethyl as a blocking group for its SBS chemistry, BGI decided to use azidomethyl in its own commercial products. *See e.g.*, Trial Tr. 277:17-278:9 (Zebra project, launched in 2015, used azido blocked nucleotides), 279:21-280:11 (BGI used Acme Biosciences to analyze Illumina's blocked nucleotides), 310:7-311:4, 312:10-16, 287:13-288:7, 309:12-310:6; TX0653 and TX0659 (BGI performed mass spectrometry and fluorescent spectra analysis on Illumina's blocking nucleotides); TX0394-002 ("(Zebra) is developed from XY [referring to Illumina]."). The copying persisted, despite BGI's dogged attempts to design-around Illumina's patents or invalidate them with its own IPR

challenges, leading to the necessity of this case and Illumina's preliminary injunction motion. TX0984, TX0985, TX0986, TX0987. Given this evidence in the record, no reasonable jury could have concluded there was clear and convincing evidence of no long-felt need, failure of others, and copying by BGI, all factors weighing heavily against the legal conclusion of obviousness as to Claim 1 of the '025 Patent.

The trial record included graphic evidence of industry praise. BGI's expert David Smith waxed eloquent about the respect for Illumina's patented technology. Dkt. No. 525-4 (D. Smith Depo. Tr.) at 97:19-98:18 ("I am a huge fan of the Illumina sequencing platform, and I applaud them for their remarkable success and the fact that they drove the $1 million cost to substantially below $1,000 -- well, two -- less than $1,000, all because of Illumina, yes."), 99:8-99:18, 112:24-113:12 (Illumina's sequencing platform "currently is the best sequencing platform on the planet because it meets all the criteria of the quality of the data and the robustness of the machines."), 178:10-182:7 ("I believe that the sequencing community holds the Illumina sequencing platform and its various components with great respect," including Illumina's azido blocking group), 203:8-204:7 (agreeing that Illumina advances in sequencing technology are "incredible advances"). Likewise, BGI's employee Dr. Snezana Drmanac testified that in 2008 when Illumina's landmark *Nature* article was published, "Illumina's azido technology caught everybody's eye," admitting industry praise. Trial Tr. 736:3-4, *see also id.* 881:21-882:8, 1060:5-25.

Skepticism that the azidomethyl blocking group would make SBS work also proves that it was far from obviousness. For example, Dr. Snezana Drmanac admitted that the sequencing community was skeptical about SBS in the 2008-2009 period. Trial Tr. 737:3-13 ("broadly in the community there was skepticism about sequencing by synthesis at that time? A. Yes. Some people would talk about that, yes."). Even in 2013 BGI and Dr. Rade Drmanac had decided to pursue a sequencing product that used a different technology, but ultimately abandoned that project in favor of copying Illumina's azidomethyl SBS technology. Trial Tr. 355:1-18, 368:13-21, 448:13-450:6 (Even though Dr. Drmanac was "familiar with the [] field" of SBS, he chose "the ligation approach, yes."); *see also id.* 1017:10-1019:1, 1059:24-1060:4.

There was further evidence of unexpected results demonstrated by the azidomethyl blocking group's success. Illumina dropped the cost of sequencing from more "more than a hundred thousand

dollars" in 2012 to "less than $600," including being the first to achieve "the thousand dollar genome" with the introduction of HiSeq X in 2014. Trial Tr. 234:1-236:7. This phenomenal decrease in the cost of sequencing was unexpected in the face of the industry skepticism, and further demonstrates the non-obviousness of the '025 Patent.

And Illumina's astonishing commercial success – with the azido technology at the heart of it – was conceded, further demonstrating their non-obviousness. *See e.g.*, Trial Tr. 236:14-237:2 (Illumina has been recognized as the world's smartest company, one of the most innovative companies, and recently, one of the most influential companies by Time Magazine), 245:25-246:6 (large research and medical institutions such as Labcorp, Quest, the Mayo Clinic, and the National Institutes of Health have purchased Illumina sequencers), 247:4-10 (noting that the NovaSeq 6000 is "pretty widely adopted" by large labs and research universities, such as UCSF and Stanford), 248:12-21 (Illumina works with influential KOLs such as Stanford, HudsonAlpha, Tempus, UCSF, and the Mayo Clinic), 1061:1-8; Dkt. No. 525-4 at 112:24-113:12.

BGI has failed to provide clear and convincing evidence to support the legal conclusion that Claim 1 of the '025 Patent is obvious such that the verdict is unsupported.

2. BGI Failed To Prove That Claim 1 Of The '025 Patent's Limitation "A Base Linked To A Detectable Label Via A Cleavable Linker" Was Disclosed In The Prior Art Or Would Have Been Obvious

There is a second independent legal defect in the jury verdict invalidating claim 1 of the '025 Patent. BGI failed to prove that the limitation "a base linked to a detectable label via a cleavable linker" was disclosed in the prior art, much less could be combined with all the other features of the claim.

Dr. Metzker's invalidity theory directed to the '025 Patent consisted of little more than the statement that the '025 Patent is "invalid in view of Parce, Zavgorodny, Kovacs, and/or Dower." Trial Tr. 862:1-3; *see generally* Trial Tr. 861:4-863:23. BGI presented no element-by-element analysis. It failed to meet its burden.

First, the Dower reference that Dr. Metzker testified was part of his invalidity analysis for Claim 1 of the '025 Patent is not even in the record and was not discussed by Dr. Metzker except as to his empty claim without identifying support that it somehow discloses "a cleavable linker." Trial Tr. 862:8-9, Trial Tr. 862:12-15 ("Q. The -- do you know where in the Dower patent, 3461, the cleavable linker

is identified, Dr. Metzker? A. I don't remember the page and line number. I don't have Dower up here."). This is a key failure of proof.

Dr. Metzker did not opine that Dower disclosed a linker attached to the ***base*** or a detectable label, much less "a base linked to a detectable label via a cleavable linker" as required by Claim 1 of the '025 Patent. Likewise, Dr. Metzker did not opine that Zavgorodny or Kovacs disclose any linkers attached to any position on a nucleic acid, whether cleavable or not, and there can be no dispute that they do not.

Thus, that leaves Parce as the only remaining potential prior art source of disclosure of "a base linked to a detectable label via a cleavable linker" in Dr. Metzker's obviousness combination. However, Dr. Metzker did not contend that there was any linker between the label and the base in Parce, much less that it was cleavable. Trial Tr. 862:17-863:2 (testifying that Parce discloses "attaching the label to the base"); JTX034 at 5:32-6:46 (description of the Formula (I) Dr. Metzker was discussing in his testimony with no reference to any linker, cleavable or not, attached to the base). During his analysis of the '973 Patent, Dr. Metzker acknowledged that, although Parce disclosed some embodiments with a cleavable linker attached to a label, not all embodiments disclosed even cleaving the label after detection. *See* Trial Tr. 853:4-16 (discussing an embodiment that uses photobleaching "instead of cleaving the linker"). Indeed, Parce specifies that for the photobleaching embodiment "a fluorescent label moiety attached, e.g., to the base, [is] preferred" (JTX034 at 18:57-58), while other embodiments disclosed with a cleavable linker attaching a label are attached to the 3' position, ***not the base***. *See* JTX034 at 15:32-40 (describing a phosphate blocking group embodiment "typically bound to the 3'-OH position" that includes a "linker moiety, which optionally comprises a detectable label" and "is typically removed by chemical cleavage."). There is no evidence in the record that Parce discloses the "base linked to a detectable label via a cleavable linker" required by Claim 1 of the '025 Patent.

Dr. Metzker was asked if his 1994 paper disclosed the cleavable linker required by the '025 Patent, and Dr. Metzker confirmed it does not discuss cleavable linkers at all. Trial Tr. 863:3-5. Dr. Metzker instead argued that that in his view "cleavable linkers were commonly known in the field by 2000," without citing to any evidentiary support in the record for that assertion and without asserting that they were ***base-connected***. Trial 863:6-8. Importantly, Dr. Metzker did not specify that cleavable

linkers attached to the base were known in the art, nor did he point to any evidence in the trial record that they were. Instead, Dr. Metzker only explained why linkers were used, and why they may be cleavable, but failed to address ***where*** the linkers could be attached or ***whether*** cleavable linkers were compatible with attachment to the base. Trial Tr. 863:9-17.

Dr. Metzker's only testimony relating to "a cleavable linker with the dye attached to the base" is a statement that such an embodiment was supposedly disclosed in the Tsien and Ju references, two references which are also not in the record. Trial Tr. 862:9-11. This is another key failure of proof. Dr. Metzker's conclusory statement about the supposed content of the prior art without citing to evidentiary support is legally insufficient. *MobileMedia Ideas LLC v. Apple Inc.*, 780 F.3d 1159, 1172 (Fed. Cir. 2015) ("Conclusory statements by an expert, however, are insufficient to sustain a jury's verdict.").

Nor can BGI properly avail itself of any supposed common knowledge in the art for such a limitation, or properly argue that Dr. Metzker's statements that the cleavable linker and attaching the label to the base were individually known in the art are sufficient. Common sense or knowledge in the art can be used to "fill in a *missing* limitation only when the limitation in question was unusually simple and the technology particularly straightforward." *DSS Tech. Mgmt., Inc. v. Apple Inc.*, 885 F.3d 1367, 1374 (Fed. Cir. 2018). Likewise, Dr. Metzker provides no explanation as to why a person of ordinary skill would be motivated to combine a cleavable linker with a label attached to the base, much less with any other elements required in Claim 1 of the '025 Patent. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("A patent composed of several elements is not proved obvious by merely demonstrating that each of its elements was, independently, known in the prior art."). This alone precludes a finding that there is clear and convincing support for the verdict's legal conclusion of obviousness.

B. There Is Not Clear And Convincing Evidence To Support The Legal Conclusion In The Jury's Verdict That Claim 3 Of The '444 Patent Is Invalid As Obvious

1. BGI Has Failed To Prove Claim 3 of the '444 Patent Is Invalid Because It Relies On Dr. Metzker's Opinions Which Ignored Robust Evidence Of Objective Indicia

The Federal Circuit has repeatedly held that "evidence rising out of the so-called secondary

considerations ***must*** always when present be considered en route to a determination of obviousness. Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075–76 (Fed. Cir. 2012). Although the Court at the JMOL stage must leave the presumed factual findings of the jury "undisturbed if supported by substantial evidence," "[o]bviousness is a question of law" based on adequately supported facts. *Apple Inc.*, 839 F.3d at 1047 (citing *Kinetic Concepts, Inc.*, 688 F.3d at 1356–57).

In providing an answer to that question of law, "[s]econdary considerations can be the most probative evidence of non-obviousness in the record, and enables the ... court to avert the trap of hindsight." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). Here, there is gaping hole in BGI's obviousness case for the '444 Patent – Dr. Metzker's admitted failure to even consider the objective indicia evidence. That failure demands a legal conclusion of non-obviousness because the objective indicia evidence cannot be ignored by the Court, and Dr. Metzker's incomplete obviousness opinions cannot support the legal conclusion in the jury's verdict.

It is undisputed that BGI and Dr. Metzker failed to address objective indicia at trial, and there is robust evidence in the record to show that the objective indicia strongly rebut BGI's obviousness case. The Federal Circuit has been clear that where "an expert purports to testify, not just to certain factual components underlying the obviousness inquiry, but to the ultimate question of obviousness, the expert must consider all factors relevant to that ultimate question," in order "to guard against this hindsight bias by appropriately considering all objective evidence of nonobviousness." *See InTouch Techs.*, 751 F.3d at 1352 (citing *In re Cyclobenzaprine,* 676 F.3d at 1079 ("The objective considerations, when considered with the balance of the obviousness evidence in the record, guard as a check against hindsight bias.").

Dr. Metzker understood that objective indicia were "part of the obviousness analysis" and knew "they need to be considered." Trial Tr. 879:24-880:11. Yet, Dr. Metzker testified again and again he did not have any opinion on the objective indicia as part of his obviousness analysis:

> Q. Okay. Do you have any opinions for trial in this case on skepticism?
>
> A. I do not appear to offer any opinion on skepticism.

> Q. Do you have any opinions for trial on the topic of unexpected results?
>
> A. I have not offered any opinions on unexpected results.
>
> Q. Do you have any opinions in this case for trial on long-felt need?
>
> A. I am not offering any opinions on long-felt need –
>
> …
>
> Q. Do you have any opinion in this case on lack of contemporaneous and independent invention by others?
>
> A. I do not offer any opinions on lack of contemporaneous and independent inventions by others in this report.

Dkt. No. 525-12 at 52:22-53:8, 53:18-23; *see also* Trial Tr. 880:18-886:23. Dr. Metzker willfully "ignored the objective evidence of nonobviousness," yet sold the jury his obviousness story. *InTouch Techs.*, 751 F.3d at 1352; *see* Trial Tr. 830:7-9 (Dr. Metzker providing "a summary of my opinions that claim 3 of the '444 Patent is invalid in view of Zavgorodny and [Kovacs].").

Nor was it a mistake that BGI decided not to face the robust objective indicia in this case. Dr. Metzker testified at trial that he did not consider the objective indicia because he was not given the "free will" by BGI's counsel "to do whatever [he] want[ed]" but instead was given a specific assignment that excluded the objective indicia. Trial Tr. 868:5-11. It was BGI's burden to put forward clear and convincing evidence to show the '444 Patent was obvious after all the evidence presented was considered, but yet it promoted its obviousness conclusion to the jury without considering the key objective evidence. *Apple Inc.*, 839 F.3d at 1048 ("A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to reach a conclusion of obviousness until all those factors are considered"). BGI's reliance on Dr. Metzker's obviousness analysis despite his failure to even address this evidence is a fatal flaw, and leaves no clear and convincing evidentiary basis for the jury to have reached the legal conclusion that either claim they found invalid is obvious.

2. The Evidence Of Objective Indicia Ignored By Dr. Metzker Is Robust And Supports A Legal Conclusion Of Non-obviousness

As described above, the jury, other Courts, and the evidence at trial conclusively demonstrate that there was not clear and convincing evidence to support a legal conclusion of obviousness under BGI's sequencing theory. *See* §§ II, IV.A.1. Among other things, the unrebutted objective indicia

renders BGI's obviousness theory legally inadequate. Illumina put forward robust evidence of long-felt need, failure of others, copying, skepticism, industry praise, and unexpected results in the sequencing realm. *See* § IV.A.1. This aligned with the previous Courts and the majority of the verdict rendered by the jury in this case, definitively demonstrating the inadequacy of BGI's sequencing theory. *Id*.

Thus, the jury's verdict with respect to Claim 3 of the '444 Patent is dependent on BGI's antiviral theory to provide the motivation to combine and reasonable expectation of success. *See also* Trial Tr. 829:20-21 (explaining that the '444 Patent "doesn't require anything else other than the group can be removed"). But regardless of the precise obviousness theory, "evidence rising out of the so-called secondary considerations ***must*** always when present be considered en route to a determination of obviousness." *In re Cyclobenzaprine,* 676 F.3d at 1075–76. The strength of the objective indicia demonstrated by the trial record cannot be discounted under BGI's alternative antiviral motivation to combine theory. "Secondary considerations can be the most probative evidence of non-obviousness in the record, and enables the ... court to avert the trap of hindsight" independent of the obviousness theory. *Crocs, Inc.,* 598 F.3d at 1310.

In addition to the robust objective indicia of non-obviousness demonstrated in the trial record with respect to the sequencing field, the real-world evidence supporting the non-obviousness of the '444 Patent that specifically rebuts BGI's antiviral theory is overwhelming, and supports a legal conclusion of non-obviousness given Dr. Metzker's willful decision to ignore it.

Dr. Metzker opined that the '444 Patent would have been obvious over Zavgorodny in view of Kovacs because in his view a POSITA "would think to use a 3 prime O azidomethyl block nucleic acid [disclosed in Zavgorodny] as an antiviral" because of its similarity with AZT, and would follow the method in Kovacs to test its antiviral activity. Trial Tr. 819:8-16, 824:3-17, 825:22-826:23. Dr. Metzker explained that "because AZT was so successful, a clinically approved drug that went into the market looking at molecules that are similar, that have the same functional groups, would actually be a good motivation of why a person of ordinary skill would want to make a nucleotide to look at other potential drugs for not just HIV, for maybe other viruses or cancer solutions." Trial Tr. 820:8-13. However, Dr. Romesberg explained and Dr. Metzker did not dispute that the 3'-O-azidomethyl

nucleoside is a 3'-O blocked ***reversible*** terminator, in contrast to AZT and other nucleoside antivirals, which are not 3'-O blocked because the functional group is attached directly to the 3'-C without any 3'-O, and are therefore ***irreversible*** terminators. Trial Tr. 1100:7-1101:4; *see also* Trial Tr. 819:17-820:7 (Dr. Metzker explaining that at the "3 prime position of AZT there is an N3 group" attached directly to the 3'-C, in contrast to 3'-O-azidomethyl, which has an additional oxygen), 827:20-828:11 (Dr. Metzker explaining that the 3'-O-azidomethyl nucleotide has a removable blocking group).

Of course, to serve as an antiviral you would ***not*** want a terminator that could be reversed to allow the virus to replicate. Given that, it is not surprising that Dr. Metzker admitted that in the history of science he was "not aware of any reversible terminator at all being used as an antiviral therapeutics." Trial Tr. 908:13-15; *see also* Trial Tr. 1039:9-1040:11 (Dr. Romesberg testifying to the same). Dr. Metzker's antiviral obviousness theory that the jury apparently relied on to invalidate Illumina's patent rests completely on the proposition that it would have been obvious to test 3'-O-aziodmethyl as an antiviral despite the fact that as far as he knew no 3'-O blocked reversible terminator has ***ever*** been used as an antiviral, even to 2021. Trial Tr. 908:13-15. BGI's primary reference, Zavgorodny, published in 1991. So that is thirty years of no evidence of anyone ever using ***any*** reversible terminator as an antiviral at all – much less the very specific molecule claimed in the '444 Patent.

As further evidence, Dr. Metzker explained that "in the three decades since Zavgorodny, 1991, there's been an enormous effort … to try to address AIDS with different therapies." Trial Tr. 907:9-13. Dr. Metzker's antiviral obviousness theory dubiously supposes that a POSITA would view the azidomethyl disclosed in Zavgorodny as one of those potential therapies, and be motivated to test it in combination with Kovacs. But at trial, Dr. Metzker testified that he was not "aware of any published work attempting to use azidomethyl for HIV as an antiviral," and had no "explanation for why" scientists or researchers had not "published [an] experiment testing azidomethyl as an antiviral." Trial Tr. 907:14-18, 908:5-9. This strong showing of a long-felt need for antiviral therapies demonstrates that the alleged motivation that Dr. Metkzer relies on exists to this day. If the '444 Patent was obvious under Dr. Metzker's theory, it stands to reason that someone would have been motivated as Dr. Metzker opined a POSITA would have been and tested it in the last thirty years – the fact the Dr. Metzker is unaware of anyone having done so is precisely the type of objective evidence that the Federal Circuit

has instructed "may often be the most probative and cogent evidence in the record" and "must always when present be considered en route to" the ultimate legal determination of obviousness. *In re Cyclobenzaprine*, 676 F.3d at 1075–76.

In contrast to Dr. Metzker's head-in-the-sand approach, Dr. Romesberg "consider[ed] all factors relevant to" his answer to "the ultimate question of obviousness" – that Claim 3 of the '444 Patent was not obvious. *InTouch Techs.*, 751 F.3d at 1352; Trial Tr. 1040:12-15 (Dr. Romesberg's conclusion that "based on everything" he testified about Dr. Metzker has not "met his burden of showing invalidity by clear and convincing evidence based on any of his antiviral theories"), 1056:12-24 (Dr. Romesberg testifying that he considered "long-felt need" along with all the other objective indicia of non-obviousness as part of his obviousness analysis for all the asserted claims, including the '444 Patent). For example, Dr. Romesberg's testimony about the actual realities of Dr. Metzker's proposed obviousness theory were unequivocal and demonstrated the failure of others – "I wanted to point out that there are no antiviral drugs that have 3 prime blocked nucleosides. There aren't any." Trial Tr. 1039:9-1040:11. Dr. Romesberg explained that he looked at the real-world evidence of testing of antivirals that was published, and found that researchers did test 3'-***C***-azidomethyl, but found it had no antiviral activity, despite also being superficially similar to AZT, demonstrating the Dr. Metzker's supposedly obvious path of the invention in the '444 Patent was a dead end. Trial Tr. 1038:12-1039:2; *see also Daiichi Sankyo Co. v. Matrix Lab'ys, Ltd.*, 619 F.3d 1346, 1354-1356 (Fed. Cir. 2010) (Despite the fact that there was "a difference of only a single oxygen atom between" the lead compound and the claimed invention, the Court found that "one of skill in the art would not have been motivated to modify" the lead compound as proposed because "the prior art as a whole taught away from" the specific modifications necessary to arrive at the claimed invention, noting that the single oxygen difference "is of greater significance than it superficially appears, as it is the difference between functional groups."). Dr. Romesberg's fully considered analysis of the ultimate obviousness question stands unrebutted by Dr. Metzker, because he failed to address "one of the four considerations" of the "obviousness analysis." Trial Tr. 880:12-17.

3. The Flaw In Dr. Metzker's Incomplete Obviousness Opinion Is Further Demonstrated By The Insufficient Evidence In The Record To Support BGI's Antiviral Obviousness Theory

In addition to Dr. Metzker's failure to opine on the objective indicia, there is also ample unrebutted evidence in the record that shows that BGI failed to meet its clear and convincing burden to show that a POSITA would have been motivated to try the 3'-O-azidomethyl nucleoside disclosed in Zavgorodny as an antiviral in combination with Kovacs. In light of the testimony from both parties' experts that no 3'-O blocked reversible terminator has ever been used as an antiviral (Trial Tr. 908:13-15, 1039:9-1040:11), it was BGI's burden to address this gap and explain why a "skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention." *PAR Pharm., Inc.*, 773 F.3d at 1192-1194; *see also Intercontinental Great Brands LLC v. Kellogg N. Am. Co.*, 869 F.3d 1336, 1344 (Fed. Cir. 2017) ("The court should consider a range of real-world facts to determine whether there was an apparent reason to combine the known elements in the fashion claimed"). BGI utterly failed to provide any evidence to support that motivation, especially in the face of the undisputed objective evidence.

First, BGI failed to put forward clear and convincing evidence to explain why a POSITA focused on developing DNA sequencing and analysis methods would have even attempted to develop an antiviral drug instead. There can be no dispute that the POSITA with respect to the '444 Patent "would be working on the research and development of DNA analysis and sequencing techniques." Trial Tr. 907:5-6. The jury was provided with both parties' POSITA definitions, both of which focused on sequencing without any mention of antiviral drug development. Dkt. No. 521 at 22 ("Illumina contends that the level of ordinary skill in the field was a member of a team of scientists ***addressing SBS product development***" and "Defendants contend that the level of ordinary skill in the field was a scientist working on the research and ***development of DNA analysis and sequencing techniques***, including the synthesis and use of labeled nucleotides."). Additionally, the '444 Patent itself is clearly focused on sequencing, describing the claimed modified nucleotides for use in sequencing at length, including a working example of the nucleotides being used in an SBS method. *See e.g.*, '444 Patent at 59:8-60:3, Figs. 5 and 6; Trial Tr. 1068:21-1071:9 (Dr. Romesberg describing the working example showing sequencing in detail); *see also* '444 Patent at 8:47-53 ("The present invention relates to nucleotide or

nucleoside molecules that are modified by the reversible covalent attachment of a 3'-OH blocking groups thereto, and which molecules may be used in reactions where blocked nucleotide or nucleoside molecules are required, such as in sequencing reactions, polynucleotide synthesis and the like."). Indeed, the '444 Patent begins by explaining "[t]he invention relates to modified nucleotides. In particular, this invention discloses nucleotides having a removable protecting group, their use in polynucleotide sequencing methods and a method for chemical deprotection of the protecting group." '444 Patent at 1:19-23. In contrast, there is no mention of antivirals of any type anywhere in the patent, much less any suggestion that the claimed molecules would have any use as antivirals, further confirming Dr. Metzker's testimony that he was "not aware of any reversible terminator at all being used as an antiviral therapeutics." Trial Tr. 908:13-15.

Given that the patent, both parties' POSITA definitions, and Dr. Metzker all agree that the POSITA was focused on developing DNA sequencing and analysis techniques, it was BGI's burden to adequately explain why the POSITA would have shifted gears to developing an antiviral drug, as Dr. Metzker's antiviral obviousness theory requires. BGI failed to do so at trial – there is not clear and convincing evidence in the record that developing an antiviral drug and performing the mechanistic studies on it is in any way related to developing DNA sequencing and analysis techniques. Instead, Dr. Metzker skipped over that crucial showing, testifying the evidence showed a "good motivation of why a person of ordinary skill would want to make a nucleotide to look at other potential drugs for not just HIV, for maybe other viruses or cancer solutions" without any explanation how that related to the problem of developing DNA sequencing and analysis techniques. Trial Tr. 820:8-13.

BGI's only attempt to connect the fields of DNA sequencing and analysis and antivirals was Dr. Metzker's testimony that both fields "use polymerases" and "nucleosides can be used as antivirals, as drugs." *See e.g.*, 815:14-816:13. But Dr. Metzker failed to explain why a POSITA working on sequencing would care that nucleosides could be used as antivirals or how developing an antiviral would further the development of the sequencing techniques they were working on.[6] Dr. Metzker's reasoning

[6] To the extent BGI argues that the ultimate motivation was to use the nucleotide developed for sequencing, that theory has been rejected by the jury, previous Courts, and is not supported by the evidence. *See* §§ II, IV.A.1.

is insufficient because it fails to explain why a POSITA would have been motivated to pursue antivirals, a different problem from developing DNA sequencing and analysis methods. *MobileMedia Ideas LLC v. Apple Inc.*, 780 F.3d 1159, 1172 (Fed. Cir. 2015) ("Conclusory statements by an expert, however, are insufficient to sustain a jury's verdict."). Indeed, Dr. Metzker treated these two problems as separate issues to be solved in separate fields, testifying that a POSITA would have been motivated to use azidomethyl as an antiviral because of its similarity to AZT, and that a POSITA would turn to Kovacs as part of mechanistic study in "rational drug design" in order to find a nucleotide that worked with a target viral polymerases, before turning to "the field of sequencing" to explain that polymerases are engineered to match nucleotide in that field. Trial Tr. 819:8-821:11. There is not clear and convincing evidence in the record that can explain why a POSITA would have made such a change in problem they were attempting to solve, and therefore BGI's antiviral theory cannot support the legal conclusion of obviousness by the jury.

Second, even assuming a POSITA would have been motivated to pursue antivirals, there is not clear and convincing evidence in the record to explain why they would have been motivated to pursue for further study the azidomethyl nucleoside disclosed in Zavgorodny out of the numerous available options. Dr. Metkzer's motivation to test an antiviral analysis consisted of little more than a cite to a sentence in Zavgorodny that states "[m]odification of the methylthiomethyl (MTM) function in O-MTM derivatives of nucleosides enable synthesis of potential antivirals" and insist that Zavgorodny "says it right there" and claim that the "paper is basically about azidomethyl" in an attempt to connect the dots. Trial Tr. 817:3-9 (quoting JTX007 at 1). Dr. Metzker did not carry BGI's burden of proving why a POSITA would even consider any 3'-O blocked ***reversible*** terminator, much less 3'-O-azidomethyl, as a potential antiviral. BGI did not explain why a POSITA would be motivated to pursue as an antiviral a completely new class of compounds that had never been used as antivirals at the time of the invention and still have not been used to this day. Trial Tr. 819:17-820:7, 827:20-828:11.

Conversely, Dr. Romesberg addressed this logical gap in Dr. Metkzer's reasoning by explaining in undisputed testimony that Zavgorodny does not disclose the types of antivirals addressed in Kovacs, but rather is directed to a different class of antivirals which are a type of polymer, not chain terminators at all – whether reversible or not. *See* Trial Tr. 1035:4-1036:18. Dr. Metzker never rebutted directly

Dr. Romesberg's testimony that a POSITA would read that sentence and the papers Zavgorodny cites to support it as teaching the use of the "O-MTM derivatives" in a completely different type of antiviral than those discussed in Kovacs, not involving azidomethyl at all. Notably, Dr. Metzker completely failed to address or even consider the articles cited by Zavgorodny, while Dr. Romesberg analyzed them from the perspective of a POSITA. *See* Trial Tr. 1035:25-1036:6 ("So I went and looked at those papers. There are two papers … [and t]hey're making these polymers. They're not nucleotides. There's no phosphorus -- there's no phosphates at all. They're certainly not substrates for a DNA polymerase."). Dr. Metzker's "conclusory statements and unspecific expert testimony" with respect to the motivation to modify Zavgorodny's azidomethyl nucleoside for use as an antiviral are exactly the type of evidence, when unsupported by the underlying evidence, that the Federal Circuit has repeatedly found to be insufficient. *TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1362 (Fed. Cir. 2019); *see also DSS Tech. Mgmt., Inc.* 885 F.3d at 1376; *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1366 (Fed. Cir. 2016). These facts demonstrate why the Federal Circuit has instructed that the "objective indicia of nonobviousness serve a particularly important role in a case, like this one, where there is a battle of scientific experts regarding the obviousness of the invention. In such a case, the objective indicia provide an unbiased indication regarding the credibility of that evidence." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1370–71 (Fed. Cir. 2012).

Lastly, the record does not support a conclusion of obviousness as to any of the other reasons BGI may attempt to rely on. For example, Dr. Metzker's conclusory testimony regarding the alleged similarities between nucleosides and nucleotides are not sufficient to meet BGI's clear and convincing burden to show a motivation to combine. Similarity alone cannot replace BGI's requirement to provide "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); *Knauf Insulation, Inc. v. Rockwool Int'l A/S*, 788 F. App'x 728, 731 (Fed. Cir. 2019) ("We conclude that a finding of a motivation to combine based on similarity of the references in this case is unsupported by substantial evidence."). Likewise, Dr. Metzker's unsupported testimony that a skilled artisan "would have immediately" converted the nucleoside in Zavgorodny to a nucleotide "without any thought whatsoever" and a POSITA "will be like, well, I can make the nucleotide, which reads directly on claim 3 of the '444

patent" does not meet legal requirement of demonstrating by clear and convincing evidence that a POSITA would have had a motivation to combine. Trial Tr. 810:8-19. The Federal Circuit has been clear that "conclusory references to [an expert's] belief that one of ordinary skill in the art *could* combine these references, not that they *would* have been motivated to do so" are insufficient to support a jury's finding of invalidity. *InTouch Techs., Inc.*, 751 F.3d at 1352.

V. CONCLUSION

For the foregoing reasons and reasons Plaintiffs previously identified and submitted to the Court, Plaintiffs respectfully request that the Court issue an order that Claim 1 of the '025 Patent and Claim 3 of the '444 Patent are not invalid, or in the alternative a new trial on the issue of validity of Claim 1 of the '025 Patent and Claim 3 of the '444 Patent.

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Respectfully submitted,

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